Title

Commentary: Beyond stressful life events and depression? – reflections on Bogdan et al. (2014)

Journal

Journal of Child Psychology and Psychiatry, 55(5)

ISSN

0021-9630

Author

Belsky, Jay

Publication Date

2014-05-01

DOI

10.1111/jcpp.12238

Peer reviewed

THE JOURNAL OF CHILD PSYCHOLOGY AND PSYCHIATRY
ACAMH THE ASSOCIATION FOR CHILD AND ADOLESCENT MENTAL HEALTH
Journal of Child Psychology and Psychiatry 55:5 (2014), pp 458–459 doi:10.1111/jcpp.12238

Commentary: Beyond stressful life events and depression? – reflections on Bogdan et al. (2014)

Jay Belsky[1,2]
[1]Department of Human Ecology, University of California, Davis, CA, USA; [2]King Abdulaziz University, Jeddah, Saudi Arabia

In light of continuing disagreement, even at the meta-analytic level, as to whether the gene- × -environment (G×E) interaction involving 5-HTTLPR and stressful life events (SLEs) predicts depression, Bogdan and associates (this issue; Bogdan et al., 2014) sought to extend research on what has become a highly controversial general (G×E) and specific (5HTTLPR×SLEs) arena of inquiry. Thus, rather than seeking to replicate this specific G×E interaction in another sample of adolescents or adults, these investigators shifted the developmental focus– to very young children, aged 3–5 years of age. This re-direction was motivated by the kindling hypothesis which stipulates that the earliest episodes of depression might be especially sensitive to environmental adversity, with later episodes very much dependent on earlier ones and less a function of later-life environmental provocation. Thus, the investigators reasoned that the controversial G×E interaction might actually prove more evident and exert a more pronounced impact early in childhood than at older ages where they have been so extensively studied.

Bogdan and associates (Bogdan et al., 2014) distinguished themselves from many others evaluating the interacting effects of 5-HTTLPR and SLEs on depression in another important way. Specifically, they questioned whether the traditional diathesis-stress framework guiding, implicitly or explicitly, most prior G×E work would prove sufficient in accounting for any G×E effects discerned. Indeed, they specifically entertained the possibility that (a) it would not just be the (diathesis-stress) case that children carrying two short alleles would be more likely than others to manifest depressive symptoms or become depressed in the face of high levels of SLEs, because (b) these homozygotes would also prove least likely to do so when they experienced few, if any, SLEs, and (c) that children carrying (one or two) long alleles would prove less susceptible to either the positive effects of few or the negative effects of many SLEs. Whatever the merits of the differential-susceptibility framework that gave rise to the second and third predictions, it needs to be noted that Bogdan and associates (this issue) were constrained in their capacity to evaluate it. And this was because in their research design, a supportive environment theorized by differential-susceptibility thinkers to yield disproportionate benefits to those carrying plasticity alleles (e.g., short alleles) was operationalized as exposure to few, if any, *stressful* life events. Others have shown that a simultaneous focus on positive life events can prove useful (Taylor et al., 2006), raising the possibility that the detected G×E interactions may have been stronger had exposure to truly positive contextual conditions also been assessed.

In order to secure a sufficiently large sample of depressed pre-schoolers to afford comparative evaluation of diathesis-stress and differential-susceptibility models of environmental action, Bogdan et al. (2014) distributed some 6,000 screening checklists to child-care settings in a moderate-sized US city. Out of almost 1500 returned checklists, 416 children passed exclusion criteria, of whom 305 enrolled in the study on whom DNA was obtained from 234, thereby defining the analysis sample—and perhaps raising questions as to the generalizability of the reported findings. Information on children's behavior, emotions and symptoms was obtained by means of a validated clinical interview, with mother or other primary caregiver also detailing children's developmental experiences (e.g. pet death, day-care change, marital conflict, parental divorce), which served as the basis for scoring exposure to SLEs.

Results proved consistent with differential-susceptibility rather than diathesis-stress thinking: (a) children homozygous for the short allele evinced greater depressive symptoms and were more likely to be diagnosed as depressed than other children when exposed to many SLEs, (b) yet manifest fewer symptoms and proved less likely to be depressed than other children when exposed to few SLEs; and (c) neither of these 'for-better' or 'for-worse' effects of SLEs emerged in the case of children carrying one or two long alleles. Significantly, the application of new model-fitting methods which directly contrast the two theoretical frameworks under consideration provided support for the 'strong' differential-susceptibility model, in which children carrying two short alleles prove susceptible to beneficial *and* adverse effects of, respectively, low and high SLE levels, with other children proving to be entirely unaffected by these contextual conditions. Notably – and

questionably – Bogdan and associates (2014) treated the model-fitting method as a post-hoc, follow-up test, having first detected a significant G×E using traditional regression methods before directly evaluating the fit of alternative theoretical models to the data. But the model-fitting method was developed as an *alternative,* not supplementary approach, one that directly tests competing hypotheses without requiring a significant G×E-interaction 'screen' before being implemented. It will be troubling, at least to its developers, if the new model-fitting approach is employed in future work as it was here.

Nevertheless, and more than anything else, what the findings from this inquiry imply is something different from what some investigators of the interaction between 5-HTTLPR and SLEs in predicting depression might infer, namely, that short alleles represent a 'genetic liability to depression' (Bogdan et al., 2014: p. X). While this certainly appears to be the case when children are exposed to many SLEs and depression is the phenotype to be explained, differential-susceptibility theorists have argued that short alleles reflect, instead, sensitivity to the environment and, thereby, susceptibility to environmental influences (i.e., developmental plasticity). What the more traditional genotype-phenotype framing (i.e., genetic liability to depression) fails to acknowledge is that there are now quite a number of studies consistent with the claim that 5-HTTLPR is a 'plasticity' gene, with short-allele carriers proving especially susceptible to a variety of developmental experiences and environmental exposures – and in a for-better-and-for-worse manner – and with respect to a variety of phenotypes, not just depression. Indeed, a recent meta-analysis of G×E findings involving 5-HTTLPR reveals this to be the case, at least with respect to white children and adolescents (van Ijzendoorn, Belsky, & Bakermans-Kranenburg, 2012).

The fact that another child-focused G×E meta-analysis shows that dopamine-related polymorphisms also function as plasticity – and not just vulnerability – genes (Bakermans-Kranenburg & van Ijzendoorn, 2011) should remind us that susceptibility to environmental influence is likely a result of multiple genes and, thus, that developmental plasticity should be treated as a phenotype in its own right (Belsky & Pluess, 2013). In fact, there is repeated indication that when putative plasticity alleles are composited to create indices of 'cumulative genetic plasticity' that dose-response relations emerge (for review, see Belsky & Pluess, 2013), reflecting the fact that the more plasticity alleles an individual carries, the more strongly they are affected—again in a for-better-and-for-worse fashion—by developmental experiences and environmental exposures. Such evidence cannot but make one wonder whether the G×E effects illuminated in the Bogdan et al. (2014) study might have been even more pronounced had additional plasticity genes, as well as additional phenotypes, been the focus of inquiry.

Acknowledgements

This article was invited by the Editors of JCPP and has been subject to internal peer review. The author has declared that he has no competing or potential conflicts of interest in relation to this article.

Correspondence

Jay Belsky, Department of Human Ecology, Human Development and Family Studies Program, University of California, Davis, One Shields Avenue, 1331 Hart Hall. Davis, CA 95616, USA; Email: jbelsky@ucdavis.edu

References

Bakermans-Kranenburg, M.J., & van Ijzendoorn, M.H. (2011). Differential susceptibility to rearing environment depending on dopamine-related genes: New evidence and a meta-analysis. *Development and Psychopathology*, *23*, 39–52.

Belsky, J., & Pluess, M. (2013). Beyond risk, resilience and dysregulation: Phenotypic plasticity and human development. *Development and Psychopathology*, *25*, 1243–1261.

Bogdan, R., Agrawal, A., Gaffrey, M.S., Tillman, R., & Luby, J.L. (2014). Serotonin transporter-linked polymorphic region (5-HTTLPR) genotype and stressful life events interact to predict preschool-onset depression: A replication and developmental extension. *Journal of Child Psychology and Psychiatry*, *55*, 448–457.

van Ijzendoorn, M.H., Belsky, J., & Bakermans-Kranenburg, M.J. (2012). Serotonin transporter genotype 5HTTLPR as a marker of differential susceptibility? A meta-analysis of child and adolescent gene-by-environment studies *Translational Psychiatry*, *2*, e147 doi:10.1038/tp.2012.73

Taylor, S.E., Way, B.M., Welch, W.T., Hilmert, C.J., Lehman, B.J., & Eisenberger, N.I. (2006). Early family environment, current adversity, the serotonin transporter promoter polymorphism, and depressive symptomatology. *Biological Psychiatry*, *60*, 671–676.

Accepted for publication: 14 March 2014